

Impact of *Helicobacter pylori* Infection on Gastric Cancer Incidence in a General Japanese Population

The Hisayama Study

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Background: Several nested case-control studies have reported the potentially causal relationship between *Helicobacter pylori* infection and the development of gastric cancer. However, there has been no prospective study evaluating this issue. The purpose of this study is to examine the impact of *H pylori* infection on gastric cancer occurrence in a general Japanese population (Hisayama, Japan) stratified according to sex, using a prospective study design.

Methods: A total of 2602 subjects aged 40 years or older (1070 men; mean age, 57 years; 1532 women; mean age, 59 years) without a history of gastrectomy or gastric cancer were classified according to the status of the serum IgG antibodies to *H pylori* and observed prospectively for 9 years from 1988.

Results: Infection of *H pylori* was more common in men (71.5%) than in women (62.5%; $P < .001$). The age-

adjusted incidence of gastric cancer for men (5.3 per 1000 person-years) was 4-fold higher than that for women (1.3; $P < .001$). In men, the age-adjusted incidence of gastric cancer was significantly higher in the subjects with *H pylori* infection than in those without it (6.2 vs 2.5; relative risk, 2.59 [95% confidence interval, 1.03-6.50]), whereas no significant difference was observed in women (1.2 vs 1.1; relative risk, 0.99 [95% confidence interval, 0.36-2.68]). These results were similar even after controlling for other risk factors in multivariate analysis. It was estimated that 40.1% of gastric cancers for men in this cohort were attributable to *H pylori* infection.

Conclusion: A significant relationship exists between infection with *H pylori* and subsequent occurrence of gastric cancer for men but not for women in this Japanese population.

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SINCE THE discovery of *Helicobacter pylori* in 1983, much research has focused on the relationship of this bacterium to gastric cancer. A number of clinical case-control studies have found positive associations between *H pylori* infection and gastric cancer.¹ In addition, 8 prospective, nested case-control studies on this issue have since been reported.²⁻⁹ Of these nested case-control studies, five^{2-4,8,9} have shown a significant association between IgG seropositivity for *H pylori* and gastric cancer, and one⁷ has shown that the risk of gastric cancer was significantly increased among subjects showing positive IgA antibodies against *H pylori*, but not among those showing positive IgG antibodies. Another 2 studies from Asian countries^{5,6} have failed to reveal a significant relationship between IgG seropositivity and gastric cancer. Since all previous studies were of cross-sectional or nested case-control design, the

possibility of selection bias could not be ruled out, and the impact of *H pylori* infection on the development of gastric cancer in a general population could not be fully evaluated. Further, a number of additional factors that might influence gastric cancer, such as smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors,¹⁰⁻¹⁴ should be taken into account when the *H pylori*-cancer association is assessed.

The Japanese population is characterized by high morbidity from gastric cancer and high prevalence of *H pylori* infection,¹⁵ especially in the middle-aged and elderly. In the present article, we report the findings of a prospective survey examining the relationship between seropositivity for *H pylori* and gastric cancer occurrence in all study subjects of a general Japanese population, with an emphasis on the effect of sex in this relationship, taking other risk factors into account.

SUBJECTS AND METHODS

THE STUDY POPULATION

Hisayama is a suburb town on Kyushu Island in the southern part of Japan, located at approximately 33° north and adjacent to Fukuoka City, a large urban center. The population of the town is approximately 7000 and has been stable for 30 years. According to the 1985 census, the age and occupational distributions of the Hisayama population were almost identical to those of Japan as a whole.¹⁶ The dietary pattern of the residents was also similar to that of the participants of the National Nutrition Survey, which selected its subjects from 300 areas throughout Japan.¹⁷

The prospective population survey on which the present study is based has been conducted in Hisayama since 1961 and is ongoing. The main purpose of this survey is to elucidate the true incidence of cardiovascular disease and its risk factors among the general population of Japan.¹⁸ We have now established 3 study cohorts aged 40 years or older, 1 each in 1961,¹⁸ 1974,¹⁹ and 1988,¹⁶ and each has been observed up to the present in the same manner.

In 1988, 2742 of the Hisayama residents aged 40 years or older (80.1% of the total population in that age group) underwent a screening examination. Serum samples were collected from each participant and stored at -20°C until an assay for *H pylori* antibodies was performed. After excluding 132 individuals with a history of gastrectomy or gastric cancer, 3 individuals with an insufficient amount of stored serum, and 5 individuals who died during the examination, a total of 2602 subjects (1070 men, mean age 57 years; 1532 women, mean age 59 years) were enrolled in the study.

FOLLOW-UP SURVEY

This population was studied for 9 years between December 1, 1988, and November 30, 1997, by repeated health checkups every 1 to 2 years. Approximately 60% of the subjects regularly returned for the checkups, whereas 141 subjects (5.4% of the total subjects) moved out of town during the follow-up period. For all subjects who did not undergo regular checkups or who moved out of town, health status was checked every year by mail or telephone. In addition, a daily monitoring system was established by the study team and local physicians or members of the Division of Health and Welfare of Hisayama. To identify new occurrences of gastric cancer in the cohort, we monitored radiographic and endoscopic study records and endoscopic biopsy records of the stomach at local clinics or general hospitals in and around Hisayama. We also checked all of the records of the annual mass screenings for gastric cancer by barium radiographic examination. Further, to find any concealed gastric cancer, an autopsy was performed on 270 (78.7%) of a total of 343 subjects who died during the follow-up period. The diagnosis of all cases of gastric cancer was confirmed by histologic examination of tissue obtained by surgery, including gastrectomy, endoscopic mucosal resection, and autopsy. The tumors were classified as either intestinal type or diffuse type, according to the classification of Laurén.²⁰ The location of the tumor within the stomach was determined through a combined evaluation of clinical and histopathologic records.

During the follow-up period, gastric cancer developed in 67 subjects (48 men and 19 women), and among them, 5 cases (7.5%) involved double gastric cancers resulting in 72 lesions. There were 3 concealed cases (4.5%) first diagnosed at autopsy. Fifty-three lesions (73.6%) were classified as intestinal type, and the remaining 19 (26.4%) as diffuse type. A total of 51 lesions (70.8%) of early cancer occurred within the mucosal or submucosal layer. The interval time from baseline to the time of diagnosis of cancer varied between 0.5 and 8.7 years (mean interval, 4.9 years).

LABORATORY TESTING AND RISK FACTOR MEASUREMENT

In 1997, serum IgG antibodies to *H pylori* were assayed by means of a quantitative enzyme immunoassay using a commercial kit (HM-CAP; Enteric Products Inc, Westbury, NY). The sensitivity and specificity of this assay are within the range of 95.0% to 98.7% and 96.4% to 100%, respectively.²¹⁻²³ Assay values were interpreted as positive, negative, or indeterminate according to the manufacturer's instructions.

To assess the independent effect of *H pylori* infection on gastric cancer occurrence, the following baseline factors in addition to age and sex were used for analysis as confounding factors: (1) information about smoking habits, alcohol intake, and history of peptic ulcer disease was obtained by means of a questionnaire administered to each subject; (2) data on dietary factors were obtained by the semiquantitative food frequency method,²⁴ and the nutritional elements were adjusted for energy intake using the method of Willet and Stampfer²⁵; (3) diabetes was revealed by medical history, glucose levels, or a 75-g oral glucose tolerance test given to most of the subjects aged 40 to 79 years,¹⁶ with plasma glucose measured by the glucose-oxidase method using a glucose autoanalyzer (Glucorode-MK2; A&T Inc, Tokyo, Japan); (4) serum cholesterol level was determined enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc, Tokyo, Japan); and (5) body mass index (BMI) (weight in kilograms divided by height in meters squared) was used as an indicator of obesity.

STATISTICAL ANALYSIS

To elucidate the sex difference in the impact of *H pylori* infection on the development of gastric cancer, we performed all statistical analyses separately for men and women. Mean values of the possible risk factors were adjusted for age by means of the covariance method and were compared among different levels of antibodies with *H pylori* using the Fisher least significant difference method. The frequencies of risk factors were compared by the Mantel-Haenszel χ^2 test after adjusting for age by the direct method. The incidence of gastric cancer was calculated by the person-year method, and its difference among *H pylori* seropositivity status was analyzed by means of the Cox proportional hazards model.²⁶ The risk factor-adjusted relative risks were also estimated using the Cox proportional hazards model. In analysis according to histologic type and location of cancer, each of the double cancers was stratified into the respective categories. All the study subjects were used as a standard population for age adjustment.

Table 1. Seroprevalence of *Helicobacter pylori* Infection by Sex and Age*

Age, y	Men (n=1 070)			Women (n=1532)		
	Seropositive	Seronegative	Indeterminate	Seropositive	Seronegative	Indeterminate
40-49	69.9 (221)	26.3 (83)	3.8 (12)	60.7 (255)*	32.9 (138)	6.4 (27)
50-59	72.7 (229)	21.9 (69)	5.4 (17)	67.1 (286)	26.1 (111)	6.8 (29)
60-69	72.4 (184)	21.7 (55)	5.9 (15)	62.7 (227)*	32.3 (117)	5.0 (18)
70-79	72.5 (103)	21.8 (31)	5.6 (8)	60.1 (137)*	33.8 (77)	6.1 (14)
≥80	65.1 (28)	20.9 (9)	14.0 (6)	53.1 (51)*	42.7 (41)	4.2 (4)
Total	71.5 (765)	23.1 (247)	5.4 (58)	62.4 (956)*	31.6 (484)	6.0 (92)

*Data are percentage (number).

†P<.05 vs seropositive men.

Table 2. Age-Adjusted Mean Values or Frequencies of Risk Factors for Gastric Cancer According to *Helicobacter pylori* Seropositivity by Sex*

Risk Factors	Men			Women		
	Seropositive (n=765)	Seronegative (n=247)	Indeterminate (n=58)	Seropositive (n=956)	Seronegative (n=484)	Indeterminate (n=92)
Age, y	57.4	56.3	60.4*	58.6	59.8	57.7
Body mass index, kg/m ²	22.9	23.0	23.4	22.9	22.9	22.9
Total cholesterol, mmol/L (mg/dL)	5.09 (196.83)	5.15 (199.15)	5.01 (193.74)	5.48 (216.94)*	5.60 (216.55)	5.65 (218.48)
Fasting plasma glucose, mmol/L (mg/dL)	5.87 (105.75)	5.87 (105.75)	5.81 (104.67)	5.61 (101.06)	5.64 (101.06)	5.65 (101.78)
Diabetes, %	13.3	13.1	14.2	8.2	11.3	9.3
Smoking habits, %	49.1	48.1	54.0	8.2*	4.9	5.0
Alcohol intake, %	32.3	28.1	34.4	1.2	1.4	2.1
History of peptic ulcer disease, %	26.5*	12.8	19.7	10.6*	7.1	3.0
Total energy intake, kJ/d (kcal/d)	7795 (1863)	7719 (1845)	7719 (1845)	6448 (1541)	6318 (1510)	6448 (1541)
Total fat intake, g/d	43.8	44.7	41.7*	48.9*	50.4	51.9
Salt intake, g/d	12.3	12.8	11.4	12.3	12.3	11.9
Vitamin A intake, IU/d	2392	2441	2416	2864	2922	2836
Vitamin B ₁ intake, mg/d	0.69	0.72	0.74	0.78	0.79	0.76
Vitamin B ₂ intake, mg/d	1.02	1.04	1.00	1.15	1.19	1.23
Vitamin C intake, mg/d	60.9	63.4	60.9	75.9	77.5	75.9
Dietary fiber intake, g/d	8.9*	9.6	8.8	10.9*	11.4	11.2

*P<.05 vs seronegative subjects.

RESULTS

Table 1 gives the seroprevalence of *H pylori* by sex and age groups. The prevalence among all age groups for men was 71.5% and was significantly higher than that for women (62.4%; $P<.001$). There were no trends in prevalence among age groups in either sex.

The age-adjusted mean values or frequencies of possible risk factors in relation to *H pylori* seropositivity are given in **Table 2**. For both sexes, the frequency of history of peptic ulcer disease was significantly higher for seropositive individuals than for seronegative ones ($P<.001$ for men; $P=.04$ for women), whereas the average dietary fiber intake was significantly lower in seropositive individuals ($P=.003$ for men; $P=.02$ for women). In addition, among women with *H pylori* infection, the frequency of smoking habits was significantly higher ($P<.02$), but the mean values of total cholesterol and dietary fat intake were significantly lower than in women seronegative for *H pylori* ($P<.04$ for total cholesterol; $P=.02$ for dietary fat intake).

The age-adjusted incidence of gastric cancer was 5.3 and 1.3 per 1000 person-years for men and women, re-

spectively; the incidence was significantly higher in men than in women ($P<.001$, **Table 3**). Whereas no significant difference in the age-adjusted incidence was found between women seropositive and seronegative for *H pylori* (1.2 vs 1.1), the incidence was significantly higher in seropositive than seronegative men (6.2 vs 2.5), with a relative risk of 2.59 (95% confidence interval, 1.03-6.50; $P=.05$; **Figure**). Among seronegative subjects, the incidence of cancer for men was 2 times higher than that for women, whereas in seropositive subjects the incidence for men increased to 5 times that of women. Because of the strength of the association, the population-attributable risk percent was also estimated in men, with the result that 40.1% (95% confidence interval, 12.4%-76.1%) of gastric cancers in men were attributable to *H pylori* infection.

The net effect of *H pylori* infection on the incidence of gastric cancer was also assessed after correction for age, BMI, serum cholesterol levels, fasting plasma glucose levels, smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors (including intake of total energy, total fat, salt, vitamin A, vitamin B₁, vitamin B₂, vitamin C, and dietary fiber) by multivari-

ate analysis using stepwise inclusion (Figure). In men, *H pylori* infection remained an independently significant risk factor for gastric cancer (relative risk, 2.90; 95% confidence interval, 1.14-7.38; $P = .03$), whereas no such association was observed in women.

We next analyzed the risk of gastric cancer by *H pylori* positivity status for men according to age at baseline, follow-up period, and location and histologic type of cancer (Table 4). The age-adjusted relative risk of *H pylori* infection for cancer in the age group of 40 to 59 years at baseline was slightly higher than that in the age group of 60 years or older (albeit not statistically significant in either age group). When analyzing the association of seropositivity and cancer in relation to the duration of follow-up, the risk of cancer significantly increased in the late period of follow-up (6-9 years) but not in the early period (0-5 years). The risk of cancer located in the distal two thirds of the stomach was significantly higher for subjects with *H pylori* infection than for those without, whereas the risk of cancer located in the proximal one third of the stomach was not significantly different. When cancer was separated according to histologic type, the magnitude of the association with *H pylori* infection was similarly high in both intestinal and diffuse types, although no statistically significant differences were found between these groups.

Table 3. Age-Adjusted Incidence of Gastric Cancer According to *Helicobacter pylori* Seropositivity by Sex*

<i>H pylori</i> Status	Men (n = 1070)		Women (n = 1532)	
	No.	Incidence	No.	Incidence
Seronegative	5	2.5	6	1.1
Indeterminate	3	5.3	2	2.5
Seropositive	40	6.2†	11	1.2
Total	48	5.3	19	1.3‡

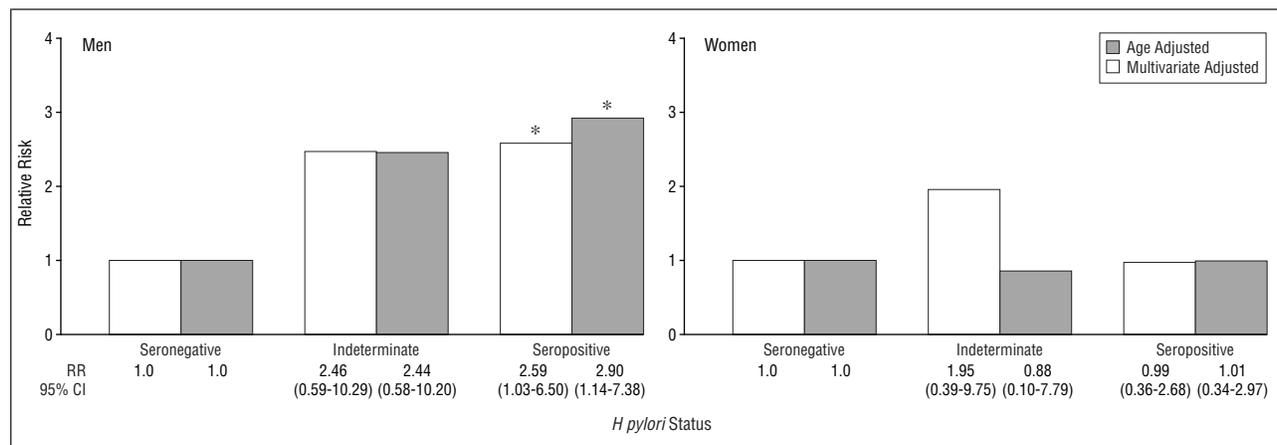
* Incidence rates are per 1000 person-years.

† $P < .05$ vs seronegative subjects.

‡ $P < .05$ vs men.

In our middle-aged and elderly subjects, the overall *H pylori* seroprevalence (71.5% in men and 62.4% in women) was higher than that in Western adult populations (around 50%),²⁷ and there was no trend toward increased prevalence by age. The high prevalence and the constancy among these age groups are consistent with the data previously reported in Japanese people born before 1949.²⁸ In the present study, *H pylori* infection was more common in men than in women. Replogle et al²⁹ also demonstrated a significantly increased risk of *H pylori* infection in men relative to women among members of the Kaiser Permanente Medical Care Program, and they also revealed a similar sex difference in infection in a meta-analysis of the seroprevalence studies. This male predominance of the infection may be attributed in part to a relative immunodeficiency for men compared with women in childhood³⁰ or to a sex difference in the frequency of lifestyle-related factors such as smoking.³¹

Previous epidemiologic studies have reported various factors related to *H pylori* infection. For example, smoking habits,^{32,33} diabetes,³⁴ and salty food intake³⁵ have been positively associated with *H pylori* infection, whereas vitamin C intake³³ has been negatively associated with the infection. These findings, however, remain controversial.³⁶⁻³⁸ In the present study, no apparent differences were found in the frequencies of diabetes and salt and vitamin C intake between the subjects with and without *H pylori* infection in either sex. In contrast, among our female but not our male subjects, there was a significant relationship between smoking habits and *H pylori* infection. The frequency of peptic ulcer disease was significantly higher in infected subjects of both sexes, but especially in men. Thus, men suffering from *H pylori*-induced peptic ulcer might tend to cease smoking because of discomfort, resulting in a disappearance of the relationship between *H pylori* seropositivity and smoking. Furthermore, in our infected subjects, the dietary fiber intake significantly decreased for both sexes, and the intake of total fat was also lower for women, which prob-



Bar graphs show age- and multivariate-adjusted relative risks (RRs) of gastric cancer according to *Helicobacter pylori* status. In multivariate analysis, age, body mass index (BMI) (weight in kilograms divided by height in meters squared), serum cholesterol levels, fasting plasma glucose levels, smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors (intake of total energy, total fat, salt, vitamin A, vitamin B₁, vitamin B₂, vitamin C, and dietary fibers) were adjusted by means of the Cox proportional hazards model using stepwise inclusion. CI indicates confidence interval; asterisk, $P = .05$ compared with seronegative subjects in the age-adjusted analysis and $P = .03$ in the multivariate analysis.

Table 4. Age-Adjusted Relative Risks of Gastric Cancer by *Helicobacter pylori* Seropositivity Status for Men According to Age at Baseline, Follow-up Period, Cancer Location, and Histologic Type*

Characteristic	No.	Relative Risk	95% Confidence Interval
Age at baseline, y			
40-59	22
Seronegative		1.0	...
Indeterminate		2.57	0.23-28.44
Seropositive		3.16	0.74-13.60
≥60 y	26
Seronegative		1.0	...
Indeterminate		2.31	0.39-13.85
Seropositive		2.20	0.65-7.38
Follow-up period, y			
0-5	18
Seronegative		1.0	...
Indeterminate		1.22	0.13-11.74
Seropositive		1.48	0.42-5.13
6-9	30
Seronegative		1.0	...
Indeterminate		4.37	0.61-31.09
Seropositive		4.25†	1.01-17.93
Location of cancer in stomach			
Proximal one third	10
Seronegative		1.0	...
Indeterminate		0.00	0.00-infinity
Seropositive		1.29	0.28-6.09
Distal two thirds	40
Seronegative		1.0	...
Indeterminate		4.12‡	0.83-20.44
Seropositive		3.66†	1.12-11.92
Histologic type			
Intestinal	35
Seronegative		1.0	...
Indeterminate		2.88	0.64-12.92
Seropositive		2.26	0.79-6.45
Diffuse	14
Seronegative		1.0	...
Indeterminate		0.00	0.00-infinity
Seropositive		2.02	0.45-9.03

*Ellipses indicate not applicable.

†P < .05 vs seronegative.

‡P < .01 vs seronegative.

ably led to the significant decline of serum cholesterol. Dyspepsia induced by *H pylori* infection may provoke changes in lifestyle, including dietary-habit changes, thereby resulting in an inconsistent relationship between *H pylori* infection and other factors.

Our study showed a significant relationship between prior infection with *H pylori* and later development of gastric cancer in male subjects. This relationship remained significant even after controlling for other risk factors in the multivariate analysis (relative risk, 2.90). The results are consistent with those of nested case-control studies, in which the odds ratios ranged from 2.5 to 6.0.^{2-4,7-9} In our male subjects, 40.1% of gastric cancers were estimated to be attributable to *H pylori* infection. This implies that, in men, 40% of gastric cancer cases may be prevented by eradication of *H pylori*. A geographical correlation study in China has also demonstrated that 40% of gastric cancer deaths could be attributed to infection by this organism.³⁹ In addition, 2 of the nested

case-control studies reported higher population-attributable risk (60%-65%).^{3,4} In these studies, the patients with cancer and the age-matched controls were thought to be older than the whole study populations from which they were selected. Thus, the prevalence of *H pylori* used in the calculation of the population-attributable risk was likely to have been overestimated, resulting in an overestimation of the cancer risk.

In our study, the stratified analysis for men showed that *H pylori* infection presented a slightly higher risk of gastric cancer among younger than among elderly subjects, and was more strongly related to tumor occurrence in the latter half of the 9-year follow-up period. These results are roughly similar to those of previous studies.^{3,7} It has been considered that the infection disappears with increasing age due to advancing atrophic gastritis, in the presence of which bacteria cannot live.⁴⁰ This would lead, in turn, to an attenuation of the relationship between *H pylori* infection and gastric cancer in the elderly and thus in the early time of follow-up.

Among our male subjects, there was a significant relationship of *H pylori* infection with cancer located in the distal two thirds of the stomach, but not with that in the proximal one third of the stomach. The lack of a relationship in the latter portion can be explained by the fact that the epidemiologic and pathologic features of cancer arising in cardia more closely resemble esophageal adenocarcinoma,⁴¹ the development of which *H pylori* does not affect.

It is widely believed that diffuse-type gastric cancer is genetically predisposed in part and less linked to environmental factors than is intestinal-type cancer.⁴² However, the relative risk of *H pylori* infection in our male subjects was similarly high for both intestinal- and diffuse-type cancer, suggesting that *H pylori* infection induces not only intestinal-type cancer, but also diffuse-type cancer with the same magnitude. Similar findings have also been reported in other epidemiologic studies.^{3,4}

In our female subjects, no significant relationship was found between *H pylori* infection and gastric cancer. Among the 4 other prospective nested case-control studies that used both male and female subjects, 2 showed similarly high odds ratios for both sexes,^{8,9} 1 showed a positive relationship only for women,⁴ and 1 showed a positive relationship only for men.⁷ These inconsistent results may be attributed to cofactors that affect the relationship between *H pylori* infection and gastric cancer. It is clear that *H pylori* infection alone cannot explain the gastric carcinogenesis. *Helicobacter pylori* infection is common, affecting around 60% to 70% of our subjects, but only a small portion of infected individuals will ever develop gastric cancer. Thus, there must be other critical cofactors affecting the risk of *H pylori* infection, and these may determine the sex difference as well as the racial and geographical differences in the infection-cancer relationship.

Several possible factors have been proposed as cofactors, for example, dietary factors, smoking, and differences in gastric acidity.^{10-13,43} We found no obvious difference in dietary factors, such as the total energy intake or total fat, salt, vitamin, and dietary fiber intakes between the sexes. Although smoking habits and alco-

hol consumption are more common in men than in women, our stratified analysis did not demonstrate an interaction between these factors and *H pylori* infection (data not shown). In addition, no apparent differences in gastric acidity between the sexes have been reported,^{44,45} and this homogeneity among sexes was thought to be extensible to the present cohort as well, although this was not proved. Thus, these factors could not explain the sex difference in the risk for our subjects.

Histologic type of gastric cancer may be another possible factor affecting the sex difference in the infection-cancer relationship. It has been proposed that *H pylori*-induced chronic inflammation leads to mucosal atrophy, intestinal metaplasia, and enhanced cell proliferation.⁴⁶ Increased proliferation may predispose a subject to carcinogenesis by increasing the likelihood of DNA mutagenesis in response to environmental carcinogens.⁴⁷ Several clinical and epidemiologic studies have reported that men have a higher risk of developing gastric cancer after severe gastric atrophy than do women.^{48,49} An experimental study also demonstrated that well-differentiated adenocarcinomas developed with a high frequency (88%) on the glandular stomach of male rats given a chemical inducer in drinking water, whereas no gastric cancer occurred in female rats given the same treatment.⁵⁰ The same study also demonstrated that the incidence of cancer was lower in castrated or estradiol-treated male rats than in nontreated male rats. These observations suggest that the relationship between chronic atrophic gastritis and gastric cancer is less pronounced in women, and that sex hormones are the crucial determinant of this sex difference. However, whereas this consideration applies to intestinal-type cancer, which develops on the basis of atrophic mucosa of the stomach, it does not apply to diffuse-type cancer, which usually occurs in the normal or slightly altered gastric mucosa. Among our 19 female subjects who developed gastric cancer, 5 had diffuse-type cancer, and all of them were *H pylori* seropositive at baseline. This indicates the possibility that *H pylori* infection was related to diffuse-type tumors but not to intestinal-type tumors in our female subjects, although a final conclusion could not be made because of the small number of each histologic type of cancer.

One of the limitations of our study is that the diagnosis of *H pylori* infection was based on a serologic test. However, it is generally agreed that IgG serology is a suitable means for screening of *H pylori* infection in large populations. The significantly higher frequency of a history of peptic ulcer disease (for which *H pylori* has been accepted as the etiologic agent⁵¹) in our *H pylori* seropositive subjects is circumstantial evidence for the validity of the serological test. However, if the misclassification of *H pylori* positivity by serologic test occurred equally among all study subjects, the risk of infection for developing gastric cancer was underestimated.

A second limitation, which is typical of most prospective studies, is that changes in other potentially confounding factors for the development of gastric cancer were not reassessed over time in our subjects. It is thus possible that modification of other risk factors occurred more in subjects with *H pylori* infection than in those without it owing to infection-induced discomfort, since these

tendencies were observed in our subjects at baseline. In this situation, the risk of cancer in infected subjects might decrease, resulting in an attenuation of the magnitude of the infection-cancer relationship. However, the carcinogenic effect of risk factors usually continues for a long period.^{12,52,53} Thus, the bias due to changes in confounding factors was considered to be small in this study.

A final limitation is that people with *H pylori* infection may be more willing to undergo upper gastrointestinal examinations owing to some nonspecific discomfort, and thus would be more likely to be diagnosed as having gastric cancer than those without infection. In this regard, the autopsy examination performed on 79% of our dead subjects should have revealed a greater number of concealed cases of gastric cancer in noninfected than in infected individuals. However, only 3 cases of cancer were first diagnosed at autopsy. This would suggest that cases of gastric cancer undiagnosed until death are rare, and that most cases of gastric cancer were detected by our follow-up system. Thus, it is reasonable to conclude that bias owing to hospital examination was scarce among the present subjects, and that observed sex differences in the incidence of cancer was not an outcome of a methodological problem.

In conclusion, our results show a significant relationship between infection with *H pylori* and subsequent occurrence of gastric cancer for men, but not for women. The higher incidence of gastric cancer in men relative to women may be explained in part by the sex difference in the impact of *H pylori* infection on gastric carcinogenesis. However, only a small percentage of persons, including men with *H pylori* infection develop gastric cancer, indicating that *H pylori* cannot be the only etiologic factor of cancer, and other cofactors must affect the relationship between *H pylori* infection and cancer. Further studies should be directed at the risk of gastric cancer among persons infected with *H pylori*.

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